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Confirmation of the Yemenite (Warburg) Deaf-Blind Hypopigmentation Syndrome

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The Yemenite deaf-blind hypopigmentation syndrome is a rare disorder characterized by severe early hearing loss, microcornea and colobomata, and cutaneous pigmentation abnormalities. A girl with similar skin symptoms and hearing loss, but no microcornea or colobomata is described and compared to other reported patients.
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INTRODUCTION

In 1990, Warburg et al. [1990] described a brother and sister from Yemen, with a "new oculo-dermato-auditory syndrome," characterized chiefly by a patchy hypo- and hyperpigmentation, sensorineural hearing loss, and eye abnormalities. We report here on a girl with strikingly similar skin and hearing problems, but less severely expressed eye anomalies.

CLINICAL REPORT

The proposita was the first of 2 children of healthy, nonconsanguineous parents. Both her younger brother and parents had normal pigmentation, vision, and hearing. The father had mild pectus excavatum. Family history was otherwise noncontributory.

Pregnancy and delivery were uneventful. Birthweight was 3,750 g (75th centile). Scalp hair was in part white at birth, skin pigmentation abnormalities became evident during the first year of life. Because of nystagmus and doubts about her hearing, she was investigated at age 9 months. Profound bilateral sensorineural hearing loss was found. Ophthalmologic and neurologic investigations did not demonstrate any abnormalities except for nystagmus. At that time, it was concluded that she probably had Waardenburg syndrome. The nystagmus disappeared spontaneously before 2 years of age.

Somatic development was influenced further by unsteady gait and mild hypertonia. No additional neurologic or vestibular studies were ever performed. Height and skull growth followed the 50th centile. Deciduous tooth eruption was mildly delayed (6 teeth at age 2 years). She proved to have mild-to-moderate learning problems, necessitating special education. Because of doubts regarding the diagnosis of Waardenburg syndrome she was re-evaluated. At 12 years she appeared

Fig. 1. Proposita at age 12 years. Note completely white anterior scalp hair, eyebrows, and eyelashes, blue irides, narrow palpebral fissures, and large upper central incisors.

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Fig. 2. Proposita. Note parietal and occipital dark blonde scalp hair below the white hair, and sharp demarcation (arrows) between hypopigmented skin and normal pigmented skin with freckles.

Fig. 3. Proposita. Note multiple freckles and several café-au-lait spots.

to be a friendly, normally intelligent girl with some behavior problems, as can be found in many deaf children. She had a slender build. Her hair was completely white in a V-shaped area running from the vertex to the forehead (Fig. 1). Her parietal and occipital hair was dark blond, whereas eyebrows and eyelashes were white. The skin of the forehead showed hypopigmentation of the anterior surface, with a sharp demarcation on the forehead and cheeks to a normal pigmented skin with multiple freckles (Fig. 2). She had a widow's peak, normal canthal distances, irregularly placed dentition, large upper central incisors but no other tooth anomalies.

There were multiple freckles on her trunk and limbs, and several larger café-au-lait spots on her trunk (Fig. 3). There was hypopigmentation of the right hand and foot, and left fingers and toes. Nails, nipples, and sweating pattern were normal. Mild pectus excavatum and somewhat tapering fingers were also noted.

Ophthalmologic investigations showed bilateral hypermetropia (+4.5 D) and markedly decreased retinal pigmentation. No nystagmus, microcornea, iris diaphania, or colobomata were noticed. Visual evoked potentials excluded misrouting of the optic nerves. An electroretinogram gave normal results. Hearing studies showed profound bilateral sensorineural hearing loss (>120 dB). Chromosomes were normal (46,XX).

DISCUSSION

The findings in the present patient are compared to those from the earlier publication [Warburg et al., 1990] and some related case reports [Lewis, 1978; Woolf et al., 1965] in Table I. Numerous entities are known in which early hearing loss is found in combination with pigmentary disorders [Reed et al., 1967; Gorlin et al., 1995]. In this respect Waardenburg syndrome is the "archetype" disorder. Both congenital, simple hypopigmentation [Telfer et al., 1971] and acquired hypopigmentation [Thurmon et al., 1976] have been described in combination with hearing loss. Congenital hypo- and hyperpigmentations with early hearing loss was described as an X-linked condition by Ziprkowski et al. [1962]. A similar disorder was described by Woolf et al. [1965] in 3 Hopi Indian brothers (see Table I). The segregation pattern of this disorder is also compatible with autosomal recessive inheritance. The distribution of the hypopigmentation is different compared to the localisation in the present patient, and, therefore, we think this to be a different entity. In 1978, Lewis [1978], in a short abstract, described changes in a large kindred with some resemblance to the presently reported patient. Unfortunately, insufficient data were provided for adequate comparison. Other reports combine skin pigmentation abnormalities and hearing loss with other symptoms, which allows easy differentiation [Jeune et al., 1963; Warburg et al., 1990; Gorlin et al., 1995].

The cause for the Yemenite deaf-blind hypopigmentation syndrome is unknown. Recently, mutations in the PAX3 gene have been found in Waardenburg syndrome type 1 [Tassabehji et al., 1992], and Waardenburg syndrome type 2 was mapped close to the human homologue of the mouse *microphthalmia* gene [Hughes et al., 1994]. Similar molecular studies in the present patient were initiated (A.P. Read, Manchester).

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TABLE I. Comparison of the Proposita With Other Published Cases With Yemenite Deaf-Blind Hypopigmentation Syndrome [Warburg et al., 1990], and Two Related Case Reports [Lewis, 1978; Woolf et al., 1965]*

	Warburg case 1	Case 2	Present patient	Lewis [1978]	Woolf [1965]
Hearing					
Early loss	70 dB	60 dB	120 dB	+	+
Eyes					
Squint	+	+	+	+	−
Nystagmus	+	+	+[a]	+	−
Photoaversion	−	−	+	+	−
Microcornea	U	B	−	−	−
Iris diaphania	+	+	−	+	−[b]
Coloboma—iris	U	B	−	−	−
—choroidea	B	U	−	−	−
Synecchiae anterior chamber	−	B	−	−	−
Ectoderm					
Patchy white hair	+	+	+	?	+
White lashes/brows	+	−	+	?	+
Hypopigmentations	+	+	+	?	+
Freckles	+	+	+	(+)	+
Café-au-lait spots	(+)	(+)	+	(+)	(+)
Taurodontia	−	+	−	?	?
Large central upper incisors	+	+	+	?	(−)
Delayed eruption tooth	+	+	+	?	?
Face					
High forehead	+	+	+	?	−
Narrow palpebral fissures	(+)	−	+	?	−
Short philtrum	+	+	+	?	−
Other					
Unsteady gait	−	−	+	+[c]	−
	High palate		Pectus excav.; tapering fingers		
Gender	F	M	F	7M/4F	3M
Pattern of inheritance	AR			AD/XL	AR/XL

* + = present; (+) = probably present; (−) = probably absent; − = absent; U = unilateral; B = bilateral.
[a] In infancy.
[b] Blue irides with very fine clumps of pigment.
[c] Vestibular abnormalities present.

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